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Zap-70 positive chronic lymphocytic leukemia co-existing with Jak 2 V671F positive essential thrombocythemia: A common defective stem cell?

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Abstract

Essential thrombocythemia (ET) co-existing with chronic lymphocytic leukemia (CLL) is extremely rare. We report two cases of ET with Jak 2 V617F in Zap-70+ CLL. ET is a myeloproliferative stem cell disease. Zap-70 expression in CLL correlates with non-mutated immunoglobulin genes. The occurrence of a less mature CLL in patients with a pluripotential stem cell disease raises the possibility that an initial “trigger hit” occurred in a pre-Jak 2 common early progenitor in these patients. Subsequent additional molecular events accumulated independently following myeloid and lymphoid differentiation, leading to the development of two diseases of likely identical origin but different lineages.

Keywords

ET; CLL; Zap-70; Jak 2 mutation

INTRODUCTION

The co-existence of two distinct clonal hematologic disorders in individual patients is rare. When this occurs, questions are often raised as to whether these two clonal disorders are related or have occurred purely out of chance. The co-existence of chronic lymphocytic leukemia (CLL) and essential thrombocythemia (ET) is very rare. There have, so far, only been five cases reported in the literature (1–5). Molecular analysis in one patient did not show the presence of Jak 2 V617F mutation in the lymphoid compartment (5). As a result, it was concluded that, at least in that patient, the CLL and ET were two independent diseases.

Here, we report two cases of Jak 2 V617F positive ET co-existing with chronic lymphocytic leukemia. The clonal B cells in both patients also strongly co-expressed the immature B-cell marker, Zap-70. Based on current understanding of Jak 2 V617F mutation in myeloproliferative diseases and Zap-70 expression in CLL, we discuss the possibility, in these two patients, of the presence of pre-Jak 2 pluripotential stem cells affected by an ‘initial genetic hit’ causing increased genomic instability and susceptibility to further genetic aberrations after lineage

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differentiation. As a result, two clonal hematologic diseases consisting of a pluripotential myeloproliferative disease and an 'immature' CLL occur within these two individual patients.

Case 1

A 72 years old male presented with nausea and unexplained weight loss over several months, associated with a moderate leukocytosis and thrombocythosis. The full blood counts showed a white cell count of 16.3 × 109/l (neutrophil 8.2 × 10^9/l, lymphocyte 7.3 × 10^9/l), hemoglobin 14.8 g/dl and the platelet count was 524 × 10^9/l. CT scan of the abdomen and pelvis showed a mild splenomegaly. Peripheral blood smear showed an absolute lymphocytosis of predominantly small mature lymphocytes with smudge cells. There was no excess of prolymphocytes. Bone marrow examination showed infiltration with small mature lymphocytes. Additionally, the marrow also showed increased numbers of magakaryocytes and early reticulin fibrosis. Cytogenetic analysis did not reveal clonal numerical or structural abnormalities. Flow cytometric studies of the B-cell population showed a clonal B-cell population co-expressing CD5/CD19 but negative for CD38 and FMC 7. These clonal B cells also strongly expressed Zap-70. Because of that thrombocytosis and the increased bone marrow reticulin staining, peripheral blood was also sent for the molecular analysis and was found to be positive for the Jak2 V617F mutation. Serum ferritin was normal. His erythrocyte sedimentation rate and C-reactive protein were not elevated. He also did not have the *bcr-abl* fusion gene by PCR. Based on these results, a diagnosis of a Zap-70+ CLL co-existing with a Jak 2 V617F positive ET was made. This patient has been treated with hydroxyurea with good clinical response. He is currently alive and has had an uneventful clinical course during the three-year follow-up.

Case 2

An 82 years old man presented initially with transient ischemic attack. Full blood count showed a normal hemoglobin, a normal white cell count of 9.1 × 10^9/l and an elevated platelet count of 762 × 10^9/l. Peripheral blood smear was essentially normal except for the presence of occasional giant platelets. In particular, he did not have any absolute lymphocytes, excess prolymphocytes or smudge cells. He also did not have any organomegaly. Bone marrow examination showed abundance of megakaryocytes occurring in clusters, with slight increase in the reticulin staining. Cytogenetic analysis did not reveal any clonal numerical or structural abnormalities. He was found to be positive for the Jak 2 V617F mutation. Serum ferritin was normal. Erythrocyte sedimentation rate and C-reactive protein were not elevated. PCR analysis for the *bcr-abl* fusion gene was negative. A diagnosis of ET was made. However, three years after the initial diagnosis, it was noted that he had progressively increasing lymphocyte count, without any organomegaly. Peripheral blood smear showed increased small mature lymphocytes with smudge cells, but without any excess of prolymphocytes. Flow cytometric analysis of the peripheral blood showed a clonal B-cell population co-expressing CD5/CD19. These B cells also strongly expressed Zap-70. Based on these results, a diagnosis of a Zap-70 + CLL in a patient with a Jak 2 V617F positive ET was made. He has been followed for seven years since the diagnosis of ET, and his platelet count is controlled on hydroxyurea.

DISCUSSION

Zap-70 is expressed in nearly 30% of CLL patients and predicts for poor prognosis (6). The Jak 2 V617F mutation is observed only in 50% of patients with ET (7). Therefore, if these two molecular events occur at random and independent of each other, one would expect the probability to be around 15% for any one individual patient and only 2% for two consecutive patients to develop both Jak 2 V617F positive ET and Zap-70+ CLL. The two patients presented in this report argue against the co-existence of the two diseases by chance, at least in these two patients.

Murine transplantation experiments using retrovirally transduced bone marrow cells suggested that the single Jak 2 V617F mutation was sufficient to induce a myeloproliferative-like phenotype (8). However, it remains unclear whether the Jak 2 V617F mutation by itself is sufficient to induce *de novo* myeloproliferative diseases. Myeloproliferative disease is a heterogeneous group of pluripotential stem cell diseases. It is highly likely that the disease represents a spectrum of clonal proliferation at varying stages of myeloid development, involving both pre-Jak 2 and post-Jak 2 pluripotential stem cells. This notion is supported by the observation that ET also occurs in patients without the Jak 2 V617F mutation. The heterogeneous stages of disease transformation of the pluripotential stem cells explain the finding, in some patients, that B cells may also be involved in the disease process (9). In some patients, the susceptibility to the development of a Jak 2 V617F mutation may require an initial genetic insult. This pre-Jak 2 genetic insult, yet to be determined, not only leads to genomic instability for the acquisition of the Jak 2 V617F mutation but also other mutations, including those of acute myeloid leukemia development. The failure to detect the Jak 2 V617F mutation in four patients who developed acute myeloid leukemia transformation of myeloproliferative disease (10) supports this notion.

We would, therefore, like to propose a model for the disease process in these two patients. We hypothesize that during the pre-Jak 2 phase of the stem cell development, an initial genetic hit occurred that predisposed the pluripotential stem cells to genomic chaos and further mutations. These genetically labile stem cells were able to differentiate into myeloid and lymphoid lineages. Once differentiated, lineage-specific independent molecular events resulted in the acquisition of the Jak 2 V617F mutation within a myeloid stem cell with subsequent growth advantage and expression of the myeloproliferative phenotype, and the malignant transformation of a B cell early in its ontogeny, before the loss of the Zap-70 molecules and any antigen stimulation to result in somatic mutation of the immunoglobulin gene. This model will explain why Jak 2 V617F mutation was not detected within the B-cell compartment in a patient with both CLL and ET (5). Whether or not this model applies to all cases of CLL co-existing with ET is unknown since the Zap-70 and Jak 2 V617F status in the other four reported cases (1–4) are not known.

In summary, it is likely that the co-existence of the CLL with ET in our patients is not by chance but to a common pre-Jak 2 stem cell affected by an initial molecular event and yet able to differentiate into different lineages. Further work involving comparison of the genetic profiles of Zap-70+ CLL cells and Jak 2 V617F positive myeloid cells from these patients with those from patients having either only Zap-70+ CLL or Jak 2 V617F positive ET may provide information needed for the molecular confirmation of our model.

References

1. Gabrail NY, Martin TW. Coexistence of essential thrombocythemia and chronic lymphocytic leukemia. Acta Haematol 1991;85:31–33. [PubMed: 2011927]
2. Marcos Sanchez F, Juarez Ucerlay F, Lobato de Blas C, Llanos del Ama ML, Duran Perez-Navarro A. Simultaneous presentation of chronic lymphocytic leukosis and essential thrombocythemia. An Med Interna 1995;12:566. [PubMed: 8804176]
3. Bizzaro N. Chronic lymphocytic leukaemia in a patient with essential thrombocythemia. Clin Lab Haematol 1998;20:377–379. [PubMed: 9951585]
4. Robak T, Urbanska-Rys H, Gora-Tybor J, Wawrzyniak E, Korycka A, Bartkowiak J, Kordek T, Polliack A. Coexistence of chronic lymphocytie leukemia and essential thrombocythemia. Leuk Lymphoma 2003;44:1425–1431. [PubMed: 12952240]
5. Henry L, Carillo S, Jourdan E, Arnaud A, Brun S, Lavabre-Bertrand T. Association of essential thrombocythemia and chronic lymphocytic leukemia: absence of the V617F Jak2 mutation in the lymphoid compartment. Am J Hematol 2007;82:500–501. [PubMed: 17301972]

6. Wiestner A, Rosenwld A, Barry TS, Wright G, Davis RE, Henrickson SE, Zhao H, Ibbotson RE, Orchard JA, Davis Z, Stetler-Stevenson M, Raffeld M, Arthur DC, Marti GE, Wilson WH, Hamblin TJ, Oscier DG, Staudt LM. Zap-70 expression identifies a chronic lymphocytic leukemia subtype with unmutated immunoglobulin gene. Inferior clinical outcome and distinct gene expression profile. Blood 2003;101:4944–4951. [PubMed: 12595313]

7. Levine RL, Pardanani A, Tefferi A, Gilliland GD. Role of JAK2 in the pathogenesis and therapy of myeloproliferative disorders. Nature Rev Cancer 2007;7:673–683. [PubMed: 17721432]

8. James C, Ugo V, Le Couedic JP, Staerk J, Delhommeau F, Lacout C, Garcon L, Raslov H, Berger R, Bennaceur-Griscelli A, Villeval JL, Constantinescu SN, Casadevall N, Vainchenker W. A unique clonal JAK2 mutation leading to constitutive signaling causes polycythemia vera. Nature 2005;434:1144–1148. [PubMed: 15793561]

9. Raskind WH, Jacobson R, Murphy S, Adamson JW, Fialkow PJ. Evidence for the involvement of B lymphoid cells in polycythemia vera and essential thrombocythemia. J Clin Invest 1985;75:1388–1390. [PubMed: 3921571]

10. Campbell PJ, Baxton EJ, Beer PA, Scott LM, Bench AJ, Huntly BJP, Erber WN, Kusec R, Larsen TS, Giraudier S, Le Bousse-Kerdiles M, Grieshammer M, Reilly JT, Cheung BY, Harrison CN, Green AR. Mutation of Jak 2 in the myeloproliferative disorders: Timing, clonality studies, cytogenetic associations, and role in leukemic transformation. Blood 2006;108:3548–3555. [PubMed: 16873677]